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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 176

[Docket No. 96F–0401]

Indirect Food Additives: Paper and Paperboard Components

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of polyamide-ethyleneimine-epichlorohydrin resin for use as a retention aid in the manufacture of paper and paperboard intended for use in contact with dry food. This action is in response to a petition filed by BASF Corp.

DATES: The regulation is effective (*insert date of publication in the* **Federal Register**); written objections and requests for a hearing by (*insert date 30 days after date of publication in the* **Federal Register**).

ADDRESSES: Submit written objections to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Vir D. Anand, Center for Food Safety and Applied Nutrition (HFS–215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3081.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of October 31, 1996 (61 FR 56242), FDA announced that a food additive petition (FAP 6B4501) had been filed by BASF Corp., 11501 Steele Creek Rd., Charlotte, NC 28273. The petition proposed to amend the food additive regulations in § 176.180 *Components of paper and paperboard in contact with*

dry food (21 CFR 176.180) to provide for the safe use of polyamide-ethyleneimine-epichlorohydrin resin for use as a retention aid in the manufacture of paper and paperboard intended for use in contact with dry food.

In its evaluation of the safety of this additive, FDA has reviewed the safety of the additive itself and the chemical impurities that may be present in the additive resulting from its manufacturing process. Although the additive itself has not been shown to cause cancer, it has been found to contain minute amounts of unreacted ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine, carcinogenic impurities resulting from the manufacture of the additive. Residual amounts of reactants and manufacturing aids, such as ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine are commonly found as contaminants in chemical products, including food additives.

I. Determination of Safety

Under the general safety standard of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. FDA's food additive regulations (21 CFR 170.3(i)) define safe as ''a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.''

The food additives anticancer, or Delaney, clause of the act (21 U.S.C. 348(c)(3)(A)) provides that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. Importantly, however, the Delaney clause applies to the additive itself and not to impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive, (*Scott* v. *FDA*, 728 F. 2d 322 (6th Cir. 1984)).

II. Safety of Petitioned Use of the Additive

FDA estimates that the petitioned use of the additive, polyamide-ethyleneimine-epichlorohydrin resin will result in exposure to no greater than 50 parts per billion (ppb) of the additive in the daily diet (3 kilogram (kg)) or an estimated daily intake (EDI) of 0.15 milligram per person per day (mg/p/d) (Ref. 1).

FDA does not ordinarily consider chronic toxicological studies to be necessary to determine the safety of an additive whose use will result in such low exposure levels (Ref. 2), and the agency has not required such testing here. However, the agency has reviewed the available toxicological data on the additive and concludes that the estimated small dietary exposure resulting from the proposed use of the additive is safe.

FDA has evaluated the safety of this additive under the general safety standard, considering all available data and using risk assessment procedures to estimate the upper-bound limit of lifetime human risk presented by ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine, carcinogenic chemicals that may be present as impurities in the additive. This risk evaluation of ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine has two aspects: (1) Assessment of the exposure to the impurities from the proposed use of the additive; and (2) extrapolation of the risk observed in animal bioassays to the conditions of exposure to humans.

A. Ethylene Oxide

FDA has estimated the exposure to ethylene oxide from the petitioned use of the additive in the manufacture of paper and paperboard to be no greater than 50 parts per quadrillion (ppq) of the daily diet (3 kg) or no more than 150 picogram (pg)/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay on ethylene oxide conducted by the Institute of Hygiene, University of Mainz, Germany (Ref. 3), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The results of the bioassay on ethylene oxide demonstrated that ethylene oxide was carcinogenic for female rats under

the conditions of the study. The test material caused significantly increased incidence of squamous cell carcinomas of the forestomach and carcinomas in situ of the glandular stomach.

Based on the agency's estimate that the exposure to ethylene oxide will not exceed 150 pg/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the proposed use of the subject additives is 2.8×10^{-10} (or 2.8 in 10 billion)) (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to ethylene oxide is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to ethylene oxide would result from the proposed use of the additive.

B. 1,4-Dioxane

FDA has estimated the exposure to 1,4-dioxane from the petitioned use of the additive in the manufacture of paper and paperboard to be no more than 55 parts per trillion (ppt) of the daily diet (3 kg) or 0.2 microgram (µg/p/d (Ref. 1)). The agency used data from a carcinogenesis bioassay on 1,4-dioxane, conducted by the National Cancer Institute (Ref. 5), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the proposed use of the additive. The results of the bioassay on 1,4-dioxane demonstrated that the material was carcinogenic for female rats under the conditions of the study. The test material caused significantly increased incidence of squamous cell carcinomas and hepatocellular tumors in female rats.

Based on the agency's estimate that exposure to 1,4-dioxane will not exceed 0.2 µg/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the proposed use of the subject additive is 6.9×10^{-9}, or 6.9 in 1 billion (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to 1,4-dioxane is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk.

Thus, the agency concludes that there is reasonable certainty that no harm from exposure to 1,4-dioxane would result from the proposed use of the additive.

C. Epichlorohydrin

FDA has estimated the exposure to epichlorohydrin from the petitioned use of the additive in the manufacture of paper and paperboard to be no more than 100 ppq of the daily diet (3 kg) or no more than 300 pg/p/d (Ref. 1). The agency used data from a Japanese carcinogenesis bioassay (Ref. 6), on epichlorohydrin fed to rats via their drinking water to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the proposed use of the additive. The results of the bioassay demonstrated that epichlorohydrin was carcinogenic under the conditions of the study. The test material caused significantly increased incidences of stomach papillomas and carcinomas in the rats.

Based on the agency's estimate that exposure to epichlorohydrin will not exceed 300 pg/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the proposed use of the subject additive is 1.4×10^{-11} (or 1.4 in 100 billion) (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to epichlorohydrin is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to epichlorohydrin would result from the proposed use of the additive.

D. Ethyleneimine

FDA has estimated the exposure to ethyleneimine from the petitioned use of the additive in the manufacture of paper and paperboard to be no greater than 2.5 ppq of the daily diet (3 kg) or no greater than 7.5 pg/p/d (Ref. 1). The agency used data from a carcinogenesis bioassay on ethyleneimine conducted by the National Cancer Institute (Ref. 7), to estimate the upper-bound limit of lifetime human risk from exposure to ethyleneimine resulting from the proposed use of

the additive. The results of the bioassay on ethyleneimine demonstrated that the material was carcinogenic for male and female mice under the conditions of the study. The test material caused significantly increased incidence of lung and liver neoplasia in both male and female mice.

Based on the agency's estimate that exposure to ethyleneimine will not exceed 7.5 pg/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the proposed use of the subject additive is 2.6×10^{-9} (or 2.6 in 1 billion) (Ref. 4). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to ethyleneimine is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to ethyleneimine would result from the proposed use of the additive.

E. Need for Specifications

The agency has also considered whether specifications are necessary to control the amount of ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine present as impurities in the additive. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low level at which ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine may be expected to remain as impurities following production of the additive, the agency would not expect the impurities to become components of food at other than extremely low levels; and (2) the upper-bound limits of lifetime risk from exposure to ethylene oxide, 1,4-dioxane, epichlorohydrin, and ethyleneimine are very low, 2.8 in 10 billion, 6.9 in 1 billion, 1.4 in 100 billion, and 2.6 in 1 billion, respectively.

III. Conclusion

FDA has evaluated the data in the petition and other relevant material. Based on this information, the agency concludes that the proposed use of the additive as a retention aid in the production of paper and paperboard is safe, and that the additive will achieve its intended technical

effect. Therefore, the agency concludes that the regulations in § 176.180 should be amended as set forth as follows.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 171.1(h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

IV. Environmental Impact

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

V. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Objections

Any person who will be adversely affected by this regulation may at any time on or before (*insert date 30 days after date of publication in the* **Federal Register**), file with the Dockets Management Branch (address above) written objection thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any

particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objection received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum from the Chemistry Review Branch, FDA, to the Indirect Additives Branch, FDA, concerning "FAP 6B4501 (MATS M2.0 & 2.1): BASF Corp., "Safe Use of Polymin SB as a Retention Agent in the Manufacture of Paper and Paperboard to be Made Into Dry Food Containers," dated September 18, 1996.

2. Kokoski, C. J., "Regulatory Food Additive Toxicology," in *Chemical Safety Regulation and Compliance*, edited by F. Homburger, J. K. Marquis, and S. Karger, New York, NY, pp. 24–33, 1985.

3. Dunkelberg, H., "Carcinogenicity of Ethylene Oxide and 1,2-Propylene Oxide Upon Intragastric Administration to Rats," *British Journal of Cancer*, 46: pp. 924–933, 1982.

4. Memorandum from the Indirect Additives Branch, FDA, to the Executive Secretary, Quantitative Risk Assessment Committee, FDA, concerning "Estimation of Upper-bound Lifetime Risk From Ethyleneimine, Epichlorohydrin, Ethylene Oxide and 1,4-dioxane in an Aqueous Solution of Either One or a Mixture of the Following Two Polymers;

Formate salt form: Hexanedioic acid with N-(2-aminoethyl)-1,3-propanediamine, aziridine, (chloromethyl)oxirane, 1,2-ethanediamine, N,N″-1,2-ethanediylbis[1,3-propanediamine] formic acid and α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [CAS Reg. No. 114133–44–7].

Sulfate salt form: Hexanedioic acid with N-(2-aminoethyl)-1,3-propanediamine, aziridine, (chloromethyl)oxirane, 1,2-ethanediamine, N,N″-1,2-ethanediylbis[1,3-propanediamine] and α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl), sulfate salt [CAS Reg. No. 16768–43–5].''Subject of Food Additive Petition No. 6B4501 (BASF Corp.), dated October 17, 1996.

5. ''Bioassay of 1,4–Dioxane for Possible Carcinogenicity,'' National Cancer Institute, NCI–CG–TR–80, 1978.

6. Konishi, Y. et al., ''Forestomach Tumors Induced by Orally Administered Epichlorohydrin in Male Wistar Rats,'' Gann 71:922–923, 1980.

7. Innes, J. R. M. et al., ''Bioassay of Pesticide Chemicals for Tumorigenicity in Mice: A Preliminary Note,'' *Journal of National Cancer Institute*, 42:1101, 1969.

List of Subjects in 21 CFR Part 176

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 176 is amended as follows:

PART 176—INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS

1. The authority citation for 21 CFR part 176 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 346, 348, 379e.

2. Section 176.180 is amended in the table in paragraph (b)(2) by alphabetically adding an entry under the heading ''List of substances'' to read as follows:

§ 176.180 Components of paper and paperboard in contact with dry food.

* * * * *

(b) * * *

(2) * * *

List of substances	Limitations
* * * *	* * *
Polyamide-ethyleneimine-epichlorohydrin resin is prepared by reacting equimolar amounts of adipic acid and three amines (21 mole percent of 1,2-ethanediamine, 51 mole percent of N-(2-aminoethyl)-1,3-propanediamine, and 28 mole percent of N, N'-1,2-ethanediylbis(1,3-propanediamine)) to form a basic polyamidoamine which is modified by reaction with ethyleneimine (5.5:1.0 ethyleneimine:polyamidoamine). The modified polyamidoamine is reacted with a crosslinking agent made by condensing approximately 34 ethylene glycol units with (chloromethyl)oxirane, followed by pH adjustment with formic acid or sulfuric acid to provide a finished product as a formate (CAS Reg. No. 114133–44–7) or a sulfate (CAS Reg. No. 167678–43–5), having a weight-average molecular weight of 1,300,000 and a number-average molecular weight of 16,000.	
* * * *	* * *

Dated: November 2, 1998

November 2, 1998

William K. Hubbard
Associate Commissioner for Policy Coordination

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

Jen Windsor

[FR Doc. 98–???? Filed ??–??–98; 8:45 am]

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